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ASBESTOS, FIBROUS MINERALS AND ACICULAR CLEAVAGE FRAGMENTS: NOMENCLATURE AND BIOLOGICAL PROPERTIES[1]

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INTRODUCTION

Inorganic Agents of Disease

Some mineral species are known to be agents of human disease (Kasik, 1970; Aponte, 1970; Langer *et al.*, 1972, Ehrenreich *et al.*, 1973a, Ehrenreich *et al.*, 1973b). They have been identified through case reports, radiographic surveys, epidemiological studies involving working populations (cohorts, case controls, prevalence and incidence surveys), and corroborative animal experimentation. The diseases associated with mineral dust inhalation include well-known clinical entities, the pneumonconioses, and also for some minerals, malignant tumors. These effects have been observed in workers engaged in mining, milling and manufacturing.

Up until some five years ago, pathogenic mineral species which had previously been identified, received attention, e.g., asbestos fibers of all varieties (International Agency for Research on Cancer, 1977), amphibole- and quartz-contaminated talcs, etc. (Rohl *et al.*, 1976). However, recently, a number of other minerals, either directly or broadly related to agents of known activity, have also been investigated. For example, single submicroscopic amphibole fibers and/or cleavage fragments which contaminate Lake Superior, have been the subject of several studies (Bowes *et al.*, 1977, Langer *et al.*, 1979). This increased interest comes about from a number of data sets viewed against an historical background.

Focus on Inorganic Fibers

The focus on inorganic fibers in the environment has come about in large part through observations made during asbestos studies. Data indicate that: (1) excess disease risk may occur with asbestos fiber exposure in circumstances other than occupational, e.g., indirect occupational (bystander in shipyards) and even in familial and environmental instances (see Langer *et al.*, 1978, Rohl *et al.*, 1977c as source references); (2) asbestos may act as a co-carcinogen to greatly increase an already elevated neoplastic risk, e.g., bronchogenic carcinoma, in cigarette-smoking asbestos workers (Selikoff *et al.*, 1968; Doll, 1971; Berry *et al.*, 1972; Hammond and Selikoff, 1973). Such increases are apparently multiplicative, suggesting, possibly, a synergistic interaction; (3) there is widespread asbestos fiber contamination of the environment, both in situations originating from specific emission sources and in situations in which there is no observable fiber used. The

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pollution is universal. Using principally chrysotile as an example, asbestos presence in numerous air and water samples has been fairly well assayed. Such monitoring has demonstrated that fiber contamination is a common occurrence (McDonald *et al.*, 1974, Selikoff, 1977; Selikoff *et al.*, 1964; Nicholson and Pundsack, 1973; Rohl *et al.*, 1977a; Rohl *et al.*, 1976, Rohl, 1975; Nicholson *et al.*, 1976; Rohl *et al.*, 1977b; Nicholson *et al.*, 1971, Selikoff, 1972; Nicholson, 1972; Biles and Emerson, 1968; Cunningham and Pontefract, 1971; Gaudichet *et al.*, 1978). The ultimate assay, human lung tissue, clearly demonstrates its ubiquity (Langer *et al.*, 1971).

Newer Observations and Hypotheses

Prior to the finding of uncoated fibers[1] in human lungs, the asbestos body was considered to be a marker for asbestos exposure. The asbestos body occurs in lung parenchyma, as well as in other organs of workers in the asbestos industries (Selikoff and Hammond, 1970). Objects similar to asbestos bodies are prevalent in lung tissues obtained from urban dwellers in the general population (Langer *et al.*, 1973). Because of this, and also the lack of direct or known asbestos exposure, some investigators discovered that other fibrous materials, not only asbestos, are nuclei for these "asbestos" bodies and a broader appellation "ferruginous body" has been often used. Inhalable materials such as fibrous pesticide excipients, fibrous glass,consumer talcs, etc., have been suggested as additional sources (Cralley, 1970). These observations tended to shift the focus from asbestos to fibrous inorganic minerals, as a class of compounds. The question was then asked: "If the coatings of asbestos bodies are nucleated on inorganic fibers other than asbestos, and a response (coating with body formation) is elicited in the host, are these fibers also not active?"

Utilizing a range of animal experiments and routes of administration, it became apparent that many varieties of inorganic fiber (of similar dimensions) not only could form "asbestos" bodies, but in contact with the mesothelial lining of the thoracic or peritoneal cavity could induce mesothelioma (Stanton and Wrench, 1972; Stanton and Layard, 1978).Following these observations, and a number of others which appeared to support the "Stanton hypothesis," (Pott and Friedrichs, 1972; Wagner *et al.*, 1973; Davis, 1976), a school of experimentalists proposed that the activity of mineral fiber was principally exerted by its morphology, and therefore morphologically similar inhalable inorganic objects are suspect as human pathogens.

Mineral Fiber in the Environment

As an outgrowth of these observations and hypotheses, the regulatory agencies, concerned with the protection of the environment, have investigated the presence of "mineral fiber" in a range of media. Acicular, or needle-like inorganic particulates either occur or have found their way into the environment, through both natural and human activites. Because asbestos is in part characterized by its morphology, and because the analytical techniques used by the regulatory agencies cannot readily distinguish among the inorganic mineral fiber species on

[1]Fiber is herein used as a morphological term only. No extrapolation is intended in terms of origin or the nature of the surface planes.

the basis of morphology alone, there has been some dispute as to the nature of the fibrous objects in these populations. This issue has often been crucial as the single factor which determined the importance of a problem.

To properly characterize needle-like inorganic particulates, a number of important problems must be addressed. In the workplace where asbestos is known to be used and where it can be characterized by relatively simple analytical techniques, problems of identification and enumeration are minor. In areas more remote from point sources where the origin of the material is unknown, problematical, or may consist of complex mineral mixtures, the difficulties involving identification and enumeration are enormous. These problems have been the subjects of three recent symposia (Asher and McGrath, 1978; Russell and Hutchings, 1978; Gravatt *et al.*, 1978).

THE NATURE OF MINERAL FIBERS, ASBESTOS FIBERS AND CLEAVAGE FRAGMENTS

The difficulties encountered in monitoring the environment for "fibers" are in part related to analytical techniques, complexity of sample, knowledge of source, etc. However, even if the mineral identity of the fibrous particle is known, another major problem arises: nomenclature. How does the investigator describe single isolated fibers, whose provenance is unknown? There has been a general lack of consistency in nomenclature which has led to confusion, so that important environmental issues have been obscured by differences in terminology, e.g., fibers have been called asbestos which may not have been asbestos; and fibers have been called "acicular cleavage fragments" which may have been asbestos. These problems may be illuminated by a discussion of nomenclatural difficulties.

The Mineral Fiber Defined

The mineral fiber which occurs in nature is the result of a process of crystallization. This object possesses an elongate habit, and may be bound by planar surfaces, formed during growth, called crystal faces. The growth of these surfaces follows kinetic, crystallographic and thermodynamic laws, and the expressed faces represent those forms which survive crystallization. These are generally planes of "least attachment energy," in that planes with the greatest attachment energy, and therefore greatest growth rates, tend to "grow out of existence." (Dowty, 1976a, Dowty, 1976b).

The fiber form is morphologically defined by an extremely high length:width ratio, superficially resembling organic fibers such as cotton and animal hair. The mineral fiber may be a single crystal, or may be composed of multiple intergrowths of single crystals, as in the case of asbestos (Campbell *et al.*, 1977, Zoltai, 1978; Thrush, 1968).

The mineralogical literature is replete with definitions concerning single fibers and composite strands. Single crystal fibers have been described as capillary, filiform, acicular, hair-like, thread-like, needle-like, etc. Nomenclature for composites of mineral fibers is more limited, with such aggregates described as fibrous, aggregates of capillaries etc. etc. The term asbestiform is also widely used, but specifically for aggregates of mineral fibers which possess distinct physical properties or condition (asbestos).

The use of the term *fibrous* connotes that the material *originated in nature through processes of crystallization*; the form observed is a "natural habit" with each single component crystal of the aggregate bound by planes formed during growth. Each of the single fiber strands posseses a high length:width ratio. A number of mineral species may possess these characteristics, including asbestos minerals. The surface exhibited by these asbestos fibers may be crystal faces, or possibly twin planes (Langer *et al.*, 1974).

Asbestos Fiber Defined

Asbestos minerals occur naturally. They are usually fibrous; have extreme length:width ratios; are flexible, possess high tensile strength, and are easily separated into filamentous strands (Zoltai, 1978). It is important to note that although most exploited asbestos deposits throughout the world possess these characteristics, there are exceptions. For example, the definition does not hold for some chrysotile deposits in California which have been described as the "Coalinga-type." In these, fibers occur as intergrown mats with few of the above characteristics visible or even measurable.

The important asbestos characteristics, which distinguishes this mineral group from fibrous rock-forming silicates, are based on its condition as determined on bulk samples (megascopic properties). It follows that examination of single submicroscopic fibers of asbestos, taken from a known specimen, may not display these important characteristics. Occasionally, when viewed by electron beam instrumentation, long amphibole asbestos fiber (greater than 20 microns in length) may show curvilinear form (Langer, 1974). However, the majority of fibers appear submicroscopically to be straight, rectilinear, sticks. Fiber tensile strength is as yet unmeasurable on this level of observation and the extrapolation of the property is by implication only (Ross, 1978). Using strict mineralogical nomenclature, isolated submicroscopic single fibers derived from *known* asbestos sources could not be termed "asbestos."

Asbestos and Amphibole Nomenclature

It is important to note that asbestos fibers are considered condition variants of common silicates (Leake, 1978), in that they are compositional and crystallographic equivalents of their rock-forming analogues but possess different physical properties. For example, the asbestos variety of the rock-forming silicate riebeckite, is crocidolite. In current usage, *asbestiform* denotes an asbestos variety of silicate fiber; it may be used as a synonym for asbestos (Campbell *et al.*, 1977; Zoltai, 1978). Although recommended, a current dictionary of geological terms suggests that asbestiform may be used to describe fibers which merely resemble asbestos (Thrush, 1978).

Confusion of nomenclature has resulted, in part, by a lack of agreement among mineralogists. The amphiboles themselves have recently come under close scrutiny by an International Commission (Leake, 1978). The recommended nomenclature for amphiboles may be used to describe asbestos and its related compounds. For example, when only the general nature of an amphibole is known, i.e., the optical properties suggest a certain mineral species but the chemical composition is unknown, then the assigned mineral name becomes an adjective which is followed by the term "amphibole." Therefore, "loosely" characterized amphiboles may be termed, e.g., grunerite amphibole. It is also recommended that for asbestos, where the approximate chemical nature of the mineral is known but not it precise composition, the recommendations made above should be followed but *amphibole* should be replaced by asbestos, e.g., grunerite asbestos. Precise mineralogical terms suggest that, for example, crocidolite may be described as (1) alkali-amphibole asbestos [uncertain mineral character]; (2) riebeckite asbestos [approximate or general nature known]; (3) magnesio-riebeckite asbestos [chemistry and character precisely known]; or asbestiform magnesio-riebeckite.

The Commission also recommends discrediting the mineral name amosite (an acronym for "Asbestos Mines of South Africa") since the originally described material was a mixture of anthophyllite and actinolite (Zoltai, 1978). Although they recommend the use of either grunerite asbestos or asbestiform grunerite, the caveat is raised that the term amosite is firmly ensconced in the biological and mining literature.

Cleavage and Cleavage Fragments Defined

For the most part, particle exposure in the workplace, and in the general environment, are to respirable comminuted objects. When inorganic mineral species are comminuted, rupture occurs along planes which for the large part are crystallographically predetermined and, in a sense, controlled. Although minerals size-reduce through parting, fracture and cleavage (Langer, 1979 in press), reduction of minerals such as amphiboles tend to be controlled by structural elements. Cleavage may be an important factor in the formation of elongate objects, in that acicular cleavage fragments are frequently indistinguishable from mineral fibers, especially on the submicroscopic scale.

Cleavage in minerals is normally defined as a planar separation occurring along crystallographic planes with the lowest surface energies. These are the planes are normally parallel to planes of the greatest net density of lattice points (greatest bond strength and density); parallel to planes of greatest d-spacing (interplanar attraction is small as compared to planar forces) and parallel to those planes of minimum surface energy. (Methods of size comminution may also play a significant role in determining how minerals "break." For example, crushing may produce abnormal cleavage planes by inducing repulsive forces on normally high surface energy planes. These local areas may produce such effects as "crack branching," etc., which may have little relationship to the crystallographic structure).

It is important to note that those faces with the lowest cleavage energy tend to be those planes with the least attachment energy. Therefore, when one compares crystal face expression on naturally-occurring fibers, one may observe that ease of formation of cleavage planes normally follow prominence of crystal face development. Crystal face development is therefore a good prediction of cleavage plane formation (Dowty, 1976a, 1976b).

Because cleavage is influenced by factors other than those of the first-order (internal structure, crystallographic control) it follows that secondary factors may become increasingly important in some instances. These secondary factors are locally controlled, and may be related to local variance in crystal chemistry, conditions of crystallization, intergrowth with other minerals, *ex solution* phenomena etc. *The same mineral species may, therefore, express different resultant forms, when subjected to identical comminutive forces*. These forms may range considerably. For example, tremolite may occur in nature as true asbestos, may be reduced to acicular cleavage fragments or equant cleavage fragments. Tremolite may, therefore, be observed with a range of habits and morphological varieties as a function of crystal-chemistry, conditions of growth, etc. These morphological variations may have associated with them different disease potentials; significantly different size distribution characteristics; differing persistence in the environment; differing inhalation potential, etc. (see discussion in Langer, 1974).

Discussion: Fibers and Acicular Cleavage Fragments

Several recent papers have presented excellent reviews concerning the terminology of mineral fiber, asbestos, and the importance of utilizing the correct nomenclature when describing these objects in the environment (Campbell, 1977; Zoltai, 1978; Ross, 1978). Concern is properly voiced amongst mineralogists, that the improper use of mineralogical nomenclature might conceivably classify many non-asbestos materials as asbestos, with the further concern that much of the mining industry will come under unnecessary attack because the current criteria used to identify "asbestos" in the environment is a "catch-all" term which may include many other substances.

Condition of fiber in nature, as a result of growth, is the only criteria for distinguishing asbestos from its rock-forming analogues. Since condition cannot be measured on single, isolated, submicroscopic fibers, strict adherence to mineralogical terminology prohibits the use of the term "asbestos" for *any* elongate amphibole encountered in the environment.

Distinction between crystal face and cleavage plane (fiber or acicular cleavage fragment) appears to be an important issue as well. Yet, the two planes tend to form along the same orientations.

Amphibole asbestos fibers tend to develop planes in nature, whether twin or face development, that differ from the cleavage planes of their rock-forming analogues. The question is begged "does this mean the biological activities of those planes are so different that a, e.g., crocidolite (asbestiform-riebeckite) (010) surface can induce mesothelioma, whereas a riebeckite (110) cannot?" (See discussion of faces and cleavage in Langer, 1979). Knowledge of the properties of asbestos is crucial in an extrapolation to "mineral fibers" as a generic group of agents with biological potential.

In the best of circumstances, it is difficult to use proper nomenclature without some degree of uncertainty. The original federal documents, which focused on problems concerning *asbestos only*, had not considered the nuances associated with application of such a standard to other areas, especially those which involved minerals which were only related to,or *resembled* asbestos. Had all the variables been foreseen current problems, which are correctly raised, might have been avoided. Yet these problems exist and should be addressed quickly. Some of these center around the following variables:

Distinction Between Cleavage Plane and Crystal Face on Particles Observed in the Evironment. Normally, the internal structure of a mineral influences the external morphology, or crystal face development. As crystal morphology is related to internal structure, so are the planes of failure (cleavage planes). As the high energy surfaces grow out of existence as a result of "attachment energy" the low energy surfaces generally remain on a crystal. Cleavage occurs in planes parallel to these low energy planes. Based on theoretical and observed cleavage plane development, the ranking of crystal faces, which appear as the result of crystallization, normally follows the ranking of cleavage plane development. Therefore, the present concern which decries the fact that minerals in the environment are "cleavage planes" and not "crystal faces" is translated into the following: such minerals observed are acicular cleavage fragments and not fibers; these mineral particles are from rock-forming silicates, and are not asbestos derived; the minerals are not asbestos, and therefore, may not be active biologically. Adherence to terminology indicates that if the original condition of the mineral is unknown, then asbestos can't be used. These caveats are indeed true. However, two shortcomings are obvious: (1) there are no data which indicate that cleavage planes are any less active than crystal faces; (2) no isolated elongate object in the environment (including asbestos) meets the mineralogical asbestos definition, *senso stricto*.

Criticism has been leveled at regulatory agencies, and their imprecise nomenclature, maintaining that strict adherence to mineralogical terms will reduce problems of lumping the non-asbestos materials with asbestos. While it is correct that an acicular cleavage fragment cannot be asbestos by definition the argument suggesting differences in biological potential between these entities is untested. For example, it is not known to what extent cations are distributed on a cleavage plane. Are the surface charges the same, are cations equally distributed, or are they non-uniform? Does the asbestos "property," which distinguishes it from its rock-forming analogue, carry down to the single fiber level? Does asbestos result from anomalous chain widths, defect structures, etc. (Veblen, 1977) or is it the result of a perfect single crystal development? (Zoltai, in press). Does asbestos, commonly indistinguishable from rock-forming silicates on the submicroscopic level, carry its peculiar properties down to the submicroscopic level?

Although there are marked cleavage differences between the amphibole asbestos minerals and their rock-forming amphibole analogues (Ampian, 1978), it is difficult to distinguish between these planes on a sublight microscopic level. There are suggestions that differences in the crystallographic axis parallel to the electron beam would produce slight variations in selected area electron diffraction patterns (Champness *et al.*, 1978; Nord, 1978). This matter is still being investigated although it is beyond the routine analysis required by regulatory agencies enforcing the asbestos standard.[1]

Aspect Ratio. There are investigators who state that the aspect ratio observed for asbestos minerals are completely different from those observed for cleavage fragments of non-asbestos minerals, e.g., Campbell *et al.* (1977). It is alleged that the regulatory 3:1 aspect ratio for "fibers" is "too small" and includes too many "cleavage fragments" in the asbestos enumeration. However, some of these determinations are based solely on light microscopy (Selikoff, 1977) and the ratios observed for standard asbestos mineral standards by electron beam instruments (especially transmission electron microscopy), includes many short "fibers" and their fragments. The relative dimensions of standard asbestos minerals observed by electron microscopy closely parallels those defined by the federal regulations (Table 2, see plates 1-3). The aspect ratio need not be the same for all fibers nor all varieties

[1]These are reports that the use of electron optical systems may be used to differentiate these forms. Data produced by Lee, *et al.*, 1978 and Champness, *et al.*, 1978 indicate that (010) (100) planes of amphibole asbestos can be differentiated from the (110), on the basis of their characteristic SAED pattern.

TABLE 1. Aspect Ratios of Respirable Fractions[1] of Selected Asbestos Samples

		Aspect Ratio With Respect to 1									
		< 5		5.1-10.0		10.1-15.0		15.1-20.0		> 20.1	
	No.	No.	%	No.	%	No.	%	No.	%	No.	%
Chrysotile[2]	340	81	23.8	86	25.3	40	11.8	24	7.0	109	32.1
Crocidolite[3]	366	173	47.3	117	32.0	39	10.7	15	4.0	22	6.0
Amosite[4]	272	107	39.3	81	29.8	31	11.4	16	5.9	37	13.6
Tremolite[5]	436	82	11.9	150	34.5	101	23.2	51	11.7	52	11.7
		Manipulation and Ratio Change									
Chrysotile[6]	554	377	68.1	158	28.5	19	3.4	0	0	0	0
Amosite[7]	248	142	57.3	90	36.3	9	3.6	7	2.8	0	0
Amosite[8]	492	421	85.6	69	14.0	1	0.2	0	0	1	0.2

[1]Water-fractionated fines. Suspension (1mg/10ml) after 15 minutes.
[2]Chrysotile: Coalinga, California. Sonified for 60 seconds, sonifer cell-disrupter, 40 watts.
[3]Crocidolite; UICC, South African, as is.
[4]Amosite: UICC, South African, as is.
[5]Tremolite: Libby, Montana. Sonified for 60 seconds, sonfier cell-disrupter, 40 watts.
[6]Chrysotile: Coalinga, California. Ball-milled at 3600 seconds.
[7]Amosite: UICC, South African. Ball-milled at 60 seconds.
[8]Amosite: UICC, South African. Ball-milled at 300 seconds.

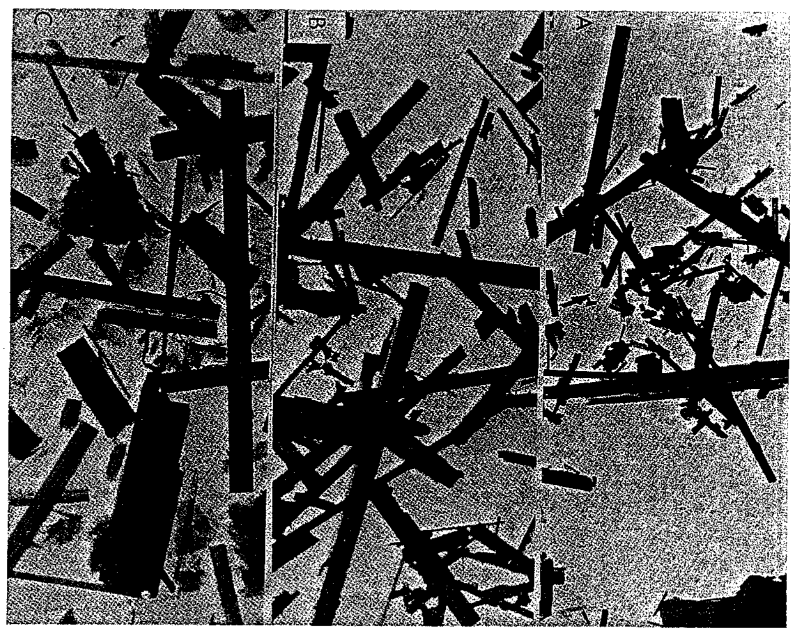

PLATE 1. The UICC Standard Reference Amphibole Asbestos Minerals: (a) crocidolite, South Africa (Kuruman area); (b) amosite, South Africa (Penge area); (c) anthophyllite, Finland. All fibers presented at approximately the same magnification (X7000-9000). The size distribution of crocidolite (both length and diameter) is skewed towards the smaller dimensions, more than amosite; amosite is skewed more than anthophyllite (see Langer *et al.*, 1974; Trimbrell *et al.*, 1970, for numerical data). Short fibers, with aspect ratios < 5:1, are numerous; fragments are common (see aspect ratio data, Table 1).

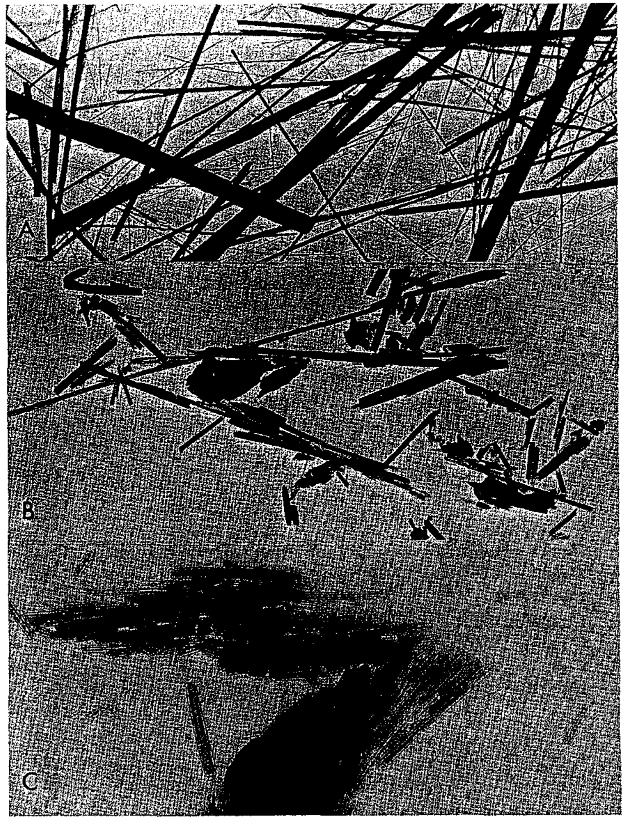

PLATE 2. Range in aspect ratio of chrysotiles from different geological sources: (a) harsh chrysotile from the Globe Region, Arizona (as is); (b) soft chrysotile fiber, number 4, from the Jeffrey Pit, Quebec (sonified 60 sec.); (c) chrysotile from Coalinga, California (sonified 300 sec.). Magnifications range from about X4,000 (A) to X21,000 (B) to X40,000 (C). The aspect ratio for the Arizona fiber is extremely great: most >100:1, all >10:1. The Canadian fiber may be size-reduced to the dimensions producing aspect ratios ranging from >100:1 to less than 5:1. The Coalinga fiber may produce "clumps" with ratios down to 2:1. Preparation technique cannot account for all of these observed differences (see Table 1). Sonification produced a size distribution of chrysotile which is frequently encountered in several work environments, e.g., the environment of automotive brake maintenance and repair operation.

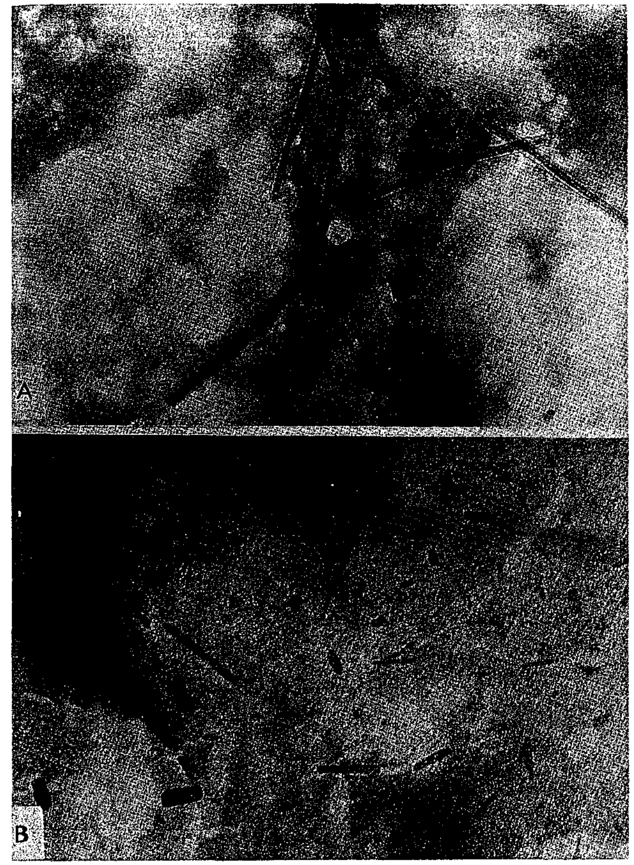

PLATE 3. Chrysotile fiber in hman tissues. Aspect ration of this single mineral species may range greatly from >> 100:1 to < 5:1. Rare cases may consist of almost 95% of fibers with aspect ratios of < 5:1 (B).

of a single fiber. In addition to these differences, alteration of fiber in any number of processes again superimposes new dimensionality, tending to first increase, and then decrease the aspect ratio dramatically. Analyses of lung tissues bear this out.

DISCUSSION

The term "asbestos" may be used to describe a mineral species only when its physical characteristics, on the megascopic level, are known: the mineral fiber possesses tensile strength, flexibility, and those other characteristics which distinguishes asbestiform minerals from their rock-forming analogues. Asbestos may also be applied to submicroscopic fibers if the source materials are known; for example, in an asbestos textile factory where chrysotile fiber is used.

Such nomenclature may also be used, with little disagreement, if environmental sampling were carried out, for example, down-wind from a known asbestos source. Fibers encountered in the tissues of humans, known to have been exposed to asbestos, may also be so categorized. Therefore, it is accurate and legitimate for the environmentalist to use specific nomenclature for submicroscopic fibers, if an asbestos source is established and if no interfering minerals occur in the sample. Identification of such materials should be based on acquisition of morphological, structural and chemical data.

When source materials are unknown or uncertain, and morphological, structural and chemical data are identical with known asbestos minerals, then the terminology should be somewhat modified. Investigators should state that mineral fibers are encountered which, on the basis of specific criteria, are identical with asbestos. However, the caveat should be inserted that their absolute identity is still insecure.

Mineral contaminants may occur in a *complex* ore deposit. For example, both tremolite and anthophyllite fiber are encountered in commercially-worked talc deposits. If the physical characteristics of the mineral fibers are known, i.e., they possess high tensile strength, and are flexible, then the term asbestos may be used. On the submicroscopic level, these physical characteristics are not measureable and the nomenclature should be modified to reflect this. for example, the use of the phrase "identical with asbestos" may be inserted as a modifier. If mineral contaminants are encountered on the submicroscopic level, and morphological, structural and chemical data are at variance with the asbestos criteria, then the more general term fiber or acicular cleavage fragment should be used, modifying the mineral name.

MINERAL PROPERTIES IMPLICATED IN BIOLOGICAL ACTIVITY

Information available about the activity of asbestos permits limited extrapolation to other types of inorganic "fibers," considered as a generic group of compounds. The subject has been reviewed extensively, and, in some instances, extrapolation has been attempted (Langer and Wolff, 1978; Stanton and Layard, 1978; Allison, 1973; Cooper, 1978; Kotin, 1978; Langer *et al.*, 1978; Nicholson *et al.*, 1978). There are a number of interesting observations made in asbestos studies which are of importance to *all* mineral particulates.

Fiber Length

Theory and observation suggest that fibers less than 5 microns in length may be completely phagocytosed *in vivo* whereas those greater than 25 microns are generally not (Allison, 1973). Intermediate size fibers, especially those near 20 microns in length, may be only partially phagocytosed or may cause thinning of the phagosomal membrane, and may, in alveolar macrophages, cause lysosomal enzymes to "leak" into the cell's cytoplasm. This inability to completely engulf "long fiber" has been called "frustrated phagocytosis" (Kuschner and Wright, 1976).

Long fibers may be responsible for cell death and the sequelae leading to parenchymal scarring; intermediate fiber lengths may also cause cell death; short fiber, although phagocytosed, tends to remain in the parenchyma.

There are extensive data to indicate that the shorter than 5 micron length fiber is by far the predominant fiber found n lung parenchyma (Langer *et al.*, 1971; Langer *et* al., 1973; Pooley *et al.*, 1970; Pooley, 1972). This is also the case for human extrapulmonary organs (Langer, 1974). Short fiber has been observed to translocate more easily than long fiber in experimental animals (Morgan, 1979). In human cases of asbestosis, the peribronchiolar and perivascular lesions, which often accompany the interstitial scarring, contain long fibers and classical asbestos bodies. Yet even in these lesions, short fiber invariably accompanies long fibers. Septal scarring may also occur between the capillary wall and the alveolar space. It is often found without significant numbers of fibers or bodies visible by light microscopy (Sebastien, 1978). Short fiber is implicated in the etiology of this lesion.

Short fiber may also be phagocytosed by attached epithelial cells (Suzuki and Churg, 1969), thereby gaining entrance into one of the target cells which may transform (bronchogenic carcinoma). Another aspect of activity recently considered is the interaction of short and long fiber in concert.

To summarize, data exist suggesting that both short ($< 5\ \mu m$) and long ($> 5\ \mu m$) fiber are biologically active. Some investigators consider that one size may be more important than the other in terms of fibrogenesis and carcinogenesis (Webster, 1969; Pott, 1978). Yet, extrapolation to fibers in the environment would suggest that, at present, all fiber lengths are suspect in producing human disease. Also, if fiber length is indeed important, then e.g., the amphibole asbestos fibers would possess different disease potentials. Crocidolite produces the shortest fiber which in South Africa has been found to be capable of producing far more mesotheliomas than, e.g., amosite (see length distributions, Langer *et al.*, 1974).

Fiber Diameter

On the basis of data obtained in animal experiments, diameter appears to play a role in the activity of asbestos fiber. The "important" diameters range from 2.5 microns down to 0.5 microns (see discussion in Pott, 1978). The importance of these dimensions may be underscored by the fact that almost *all* respirable asbestos fiber (certainly the amphiboles) occurs with diameters less than 2.5 microns (greater than 99% by number) (Langer *et al.*, 1974; Pooley *et al.*, 1970; Timbrell *et al.*, 1970).

Fiber diameter tends to correlate with other important parameters, i.e., particle number and total exposed surface area. Correlation of these parameters with activity tends to negate the simple influence of a "mass" factor (the common units used in classical toxicology in determining magnitude of response).

"Thick" (and long) fibers, constituting a mass "toxin," tend to produce less resonse when compared to an identical mass composed of "thin fibers." Diameter reduction reflects an increase in particle number and surface area per unit mass of material. Extrapolation to fibers in the environment suggests that any diameter less than several microns should be considered to be in the "active" size range. Small diameter fibers should be considered potentially active, especially in terms of carcinogenicity. Since these fibers are submicroscopic, they may be visualized and enumerated only by electron beam instruments.

Fiber Number

It is widely accepted that for two equivalent masses of mineral material (if crystal-chemical parameters are also identical), the specimen with the greatest number of particles tends to be the most active. It has been suggested that the initiation of cell transformation appears to require a finite number of particles, in contact with a specific number of target cells, for a specified period of time. Each animal, cell-type and fiber type appears to have its own set of conditions and requirements. As an example, in the rat, intraperitoneal tissues require at least 10^8 fibers of asbestos, where the "potency" of the fiber is strong, for mesothelioma induction (Pott, 1978). The tumor rate (incidence) is directly related to *fiber number* in this model. Fiber number reflects dose, in that it represents the number of fiber "hits" per cell. It reflects, in part, a possible threshold, but only if time is neglected.

Size reduction and increase in particle number (per unit mass) have been shown to improve reaction kinetics in chemical systems. For minerals in experimental systems in which the activity of the particle is being determined, size reduction may alter a number of important factors. For example, size comminution may be accompanied by decrease in fiber length and increase in phagocytosis potential. In this instance an increase in fiber number is also accompanied by a decrease in residence time in the target organ. Other characteristics which may be altered include surface properties, bond character and crystallographic characteristics (Langer *et al.*, 1978). Therefore, increase in particle number may in some instances, increase activity, but in others, may sharply reduce activity. Where fiber mass changes, for fibers within a narrow size range, greatly enhanced responses may be produced. For example, unpublished data by Dr. Charles Gold (Gold, 1970) indicate that the number of asbestos bodies present per unit mass of lung parenchyma correlates with degree of scarring (grade of asbestosis). This tends to support the observation that increased dose (mass) of fiber, increases biological responses. Yet asbestos bodies tend to form primarily on long fibers, and amphibole fibers (the study was conducted with light microscopic techniques). No correlation was observed for the number of bodies in lung tissues and the presence of malignant tumors. Hence, the concept of fiber number, fiber size, and activity, is extraordinarily complex. Absolute number and activity may not be equal for all fiber types; may not be equal for all disease entities.

Fiber Retention (size and stability)

When fiber reaches the terminal bronchioles and alveolar spaces of the lung parenchyma (a function of size, i.e., length and diameter) a number of factors may influence its retention. Fiber size is of first order importance, in that phagocytosis is obviously controlled to a large extent by particle length. Short fiber engulfed by macrophages, tend to be removed, but retention is obviously enhanced for short fiber phagocytized by attached epithelial cells. According to theory, long fibers are those which tend to be retained. Yet here again, examination of human tissues, even after an extensive lapsed period since last exposure, demonstrates that short fiber numerically predominates in the particle population (Langer *et al.*, 1971; Langer *et al.*, 1973; Pooley *et al.*, 1970; Pooley, 1972; Sebastien, 1978). Clearly, many short fibers are not removed, regardless of the time which has elapsed since last exposure.

Retention may also be in part related to stability of fiber *in vivo*. It has been demonstrated that asbestos fiber chemically and physically degrades *in vivo* (Suzuki and Churg, 1969; Langer, 1970; Langer *et al.*, 1972a; Langer *et al.*, 1972b; Morgan and Holmes, 1970). The degradation of chrysotile is greatest, followed by anthophyllite, amosite and crocidolite, in that order. The factor which controls this pattern of degradation is magnesium loss from the fiber (Langer *et al.*, 1972). This observation has been corroborated in many laboratories using a variety of analytical techniques, e.g., tracing a daughter decay products of neutron-activated fiber instilled into laboratory animals (Morgan and Holmes). It is hypothesized, basing asbestos activity as a "solid state" tumorigenic effect, that resistance to degradation is of prime importance in inducting cancer (Pott, 1978). This appeals to a number of investigators in that amphibole tumor induction, especially for mesothelioma, is thought to be greatest for those chemically resistant fiber types (Wright, 1978). Comparison of relative mesothelioma incidences in working populations exposed to the different fiber types have been interpreted as supporting this hypothesis. Caveats should be raised here: this holds only for mesothelioma; excess human bronchogenic carcinoma and gastrointestinal cancer do not appear to follow this "stability order," animal experimental data do not readily support this, in that the calculated carcinogenicity index for chrysotile exceeds all other fibers in the same experimental model (Wagner *et al.*, 1973; Wagner, 1974). On the other hand, fiber dissolution and degradation *in vivo* may impart the active quality to the fiber (Langer *et al.*, 1978). Chrysotile proton migration, magnesium leaching and silica surface (tridymite-like) may have profound biological significance. There is no evidence to support the hypothesis that degradation of fiber *in vivo* imparts a significant protective effect to the host. Although particle persistence in the host likely increases the period of cellular contact and "delivered dose" and persistence at the cellular level appears to induce alterations which lead to disease processes, the processes resulting in *in situ* degradation may also produce adverse sequelae.

Fiber Translocation and Migration

Fiber inhalation is accompanied by host response and defense (Kilburn, 1978). Particles entrapped on the mucosal surface of the nasopharynx may be swallowed and ingested and then eliminated. Inhalation may result in particle deposition in the tracheobronchial tree, or in the alveolar space, where particles may initiate macrophage response, or may be eliminated by the "mucocilliary escalator." Macrophage death may occur. At any stage particles may enter the blood stream and be hematogenously distributed throughout the host and come to rest in other organs or by lymphatical transport be sequested in nodes (Kilburn, 1978). Asbestos fibers and bodies have been found in every extrapulmonary tissue thus far examined (Langer, 1974). Although phagocytosis of long fibers may be vigorous in the trancheobronchial tree, short fibers in the alveolar spaces are associated with other responses. Here, elimination is slower and "less definite." Fibers may enter the interstitium between alveolar surface and the capillary wall, where a fibrotic response has been observed to follow (Suzuki and Churg, 1969).

Careful electron micorscopic studies, comparing sizes of asbestos fibers in lung parenchyma with those in the pleural or extrapulmonary organs, shows transmigrated fibers to be of the short lengths and diameters (Langer, 1974; Morgan, 1979; Sebastien, 1979). Most are in the submicroscopic size range. Recent data suggest excess malignancies occur in some of these organs (International Agency for Research on Cancer, 1977).

Fibrous particles observed as natural or introduced contaminants in the evironment are not restricted in their effects to a single potential target organ. Although direct transport to the lung is generally the initial and most likely target, removal from the lung may, in a proportion, indicate only translocation from one site to another. Since short fiber translocates more readily than long fiber, this fraction is preferentially mobilized. These factors hold for all inorganic fibers. Short fibers encountered in the environment may therefore be expected to lodge in organs other than lungs.

Dose

The delivered dose to an organ (e.g., the lung) may be measured as the product of the number of particles entrapped in the organ and their residence time at the target. Dose is therefore related to factors such as size, areosol stability, shape, penetration, deposition, retention, resistance to degradation, etc. (Langer and Wolff, 1978). Classical toxicological "dose-response" relationships may not hold in exactly the same manner for inorganic particles as it does for metals and organic substances (see above discussions).

The observation has been made that the risk of bronchogenic carcinoma decreases proportionately with decreased duration of fiber exposure (Seidman *et al.*, 1979 in press). In addition the lapsed period required for tumor incidence to peak is *increased* as well. Data suggest a dose-response relationship for lung cancer and asbestosis, but not as clearly for mesothelioma. Excess risk of bronchogenic carcinoma in asbestos workers is mostly confined to cigarette smoking individuals. yet for other diseases, e.g., mesothelioma, epidemiological data do not reveal a parallel parallel relationship.

In addition to mass, fiber residence time in tissue is a major factor in "dose." Some fiber is phagocytized, and "removed" (eliminated or translocated to another organ), hence the residence time is reduced and the corresponding "dose" is reduced. Yet some fiber persists, and the residence time is prolonged until the death of the individual. Thus the dose actually "increases" with time from onset of exposure, and small fiber mass, over long lapsed periods, may result in high doses or exposures.

It is known that mesothelioma may occur in individuals with very little exposure, apparently much less than occupational concentrations. Many years later, often 25 to 40 years, without additional fiber inhalation, tumors develop. Here, dose is effectively increased by the greatly protracted lapsed period from onset of exposure. An exposure of two fibers/cm^3 for a 40-year-old worker may result in a different risk than that for an 18-year-old with an equivalent exposure, other factors being equal. The latter receives a greater dose due to his increased life expectancy. These factors should be considered with inorganic fibers.

DISCUSSION

If the above factors play some role in the occurrence of human disease, then the following must be considered:

> The different amphibole asbestos fiber varieties, and chrysotile from different mines or geological localities may possess different biological potentials, per unit mass of fiber. Since fiber length and fiber number differ markedly, the delivered dose per target cell and organ will be different. Each fiber may carry with it a different disease potential.

Crocidolite, with the greatest number of short fibers per unit mass of material, could be said to be quickly phagocytosed and removed from the lung. Yet, conversely, it produces marked fibrosis (when compared with equivalent masses of other asbestos fiber) frequent mesothelioma and no reported difference in patterns of bronchogenic carcinoma or other asbestos diseases (see Davis *et al.*, 1978, for discussion). Clearly, fiber length cannot be the only factor, in producing human disease.

The work of Wagner and colleagues (Wagner *et al.*, 1973) indicates that equivalent masses of *short* fiber of crocidolite, rather than long fiber, produces the greatest numbers of mesotheliomas in laboratory animals. This, in conjunction with Pott's (1978) concept of fiber numbers required for inducing neoplastic response appears to further call attention to the importance of short fiber.

The same standard for all asbestos fiber varieties is a simplifiction but there are no useful data at present to suggest an alternative approach, especially since each mineral species may vary from locality to locality, with resultant differing size distribution. All factors influencing biological activity will therefore range greatly. Standards for single fibers do not reflect these variations, but the complex biological potentials associated with such changes cannot be encompassed in other than an overall approach, from a practical point of view.

CONCLUSIONS

There are many reports concerning the contamination of the environment with agents introduced through human activity. Among these, mineral particles have figured prominently, especially mineral fibers. This interest stems from wide range of problems delineated in asbestos research, data which has accumulated over the past seven decades. Asbestos disease has been described in occupational, para-occupational, environmental and familial settings. Excess cancer is common in these groups and may occur in both pulmonary and extra-pulmonary organs. One of the objects commonly used as an exposure index is the "asbestos" body. Observed in the lung parenchyma of asbestos-exposed individuals, they were more recently found to be present in the lung parenchyma of individuals in the general population. The use of asbestos fiber is widespread and has prompted numerous studies which have focused on fiber contamination in a range of media. The most commonly used fiber in North America, chrysotile, has been observed to be a ubiquitous environmental contaminant.
chrysotile, has been observed to be a ubiquitous environmental contaminant.

Yet, the use of the "asbestos" body as an index of exposure is hampered by the observation that other mineral fibers may form identical objects *in vivo*. This has prompted several of laboratory investigators to examine the generic group of mineral fibers (other than asbestos) in a number of test systems. Some of these have produced malignant tumors in animals, and these results have been interpreted to mean that any inorganic fiber, in contact with specific target cells, may be capable of inducing a neoplastic response.

The complexity and ramifications of the asbestos problem may be illustrated by the contamination of Lake Superior by "asbestos" (grunerite fiber). A group of mineral fibers, broadly related to, and in some instances, indistinguishable from asbestos by electron microscopy, were observed contaminating public water supplies taken from Lake Superior. This problem focused attention on a number of important issues which had never previously been addressed. These issues centered on the relationship of asbestos to other rock-forming minerals, both fibrous and non-fibrous; the nomenclature of asbestos, as related to mineral cleavage; differences in instruments and identification methodologies used by various laboratories; surface activity of minerals; differentiation between crystal face and cleavage planes in terms of biological activity; the significance of aspect ratio found in microscopic and submicroscopic fibers.

Strict adherence to mineralogical nomenclature permits the use of the terms "asbestos" only when the mineral occurs naturally as a fiber, possesses high tensile strength, and fiber flexibility. Yet, in all environmental, and most occupational settings, these characteristics are unmeasurable (particularly for individual fibers). Terminology should therefore be modified to accommodate these realities. The biological activity of mineral surfaces, including crystal faces, cleavage planes and non-crystallographically controlled partings, is under investigation. Current distinctions in terminology are perhaps less important since they are not based on biological evidence.

Other fiber characteristics, including diameter, length, numbers, dose, etc., are also currently under study. Biological activity is not restricted to a particular fiber length or diameter. The aspect ratio of different asbestos minerals varies systematically and is also a function of superimposed manipulation or processing. The current federal use of the 3:1 aspect ratio appears inclusive, so that most of the asbestos fragments are counted in this size range. Unfortunately, this tends to incorporate much "non-asbestos" mineral into the asbestos category. The study of fibers, other than asbestos, should be intensified.

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Severe asbestosis: 500, 000-13,000,000 asbestos bodies per gram
Moderate asbestosis: 100-500,000 asbestos bodies per gram
Mild asbestosis: 10-100,000 asbestos bodies per gram
Doubtful asbestosis: 10-15,000 asbestos bodies per gram
No disease: < 10,000 asbestos bodies per gram
No correlation observed for asbestos body content and tumors: 13,000-13,000,000 asbestos bodies per gram

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